REMARKS

The Invention

The invention features methods for treating neurodegenerative disorders by transplanting into patients lineage-restricted progenitors generated from embryonic stem cells. The stem cells are transformed, *ex vivo*, to express one or more cell fate-inducing genes (e.g., Nurr-1 or PTX3) which direct their differentiation into a neuronal or glial cell type. These transformed cells are transplanted into the nervous system of the patient. Suitable cell fate-inducing genes are disclosed in the specification.

Support for Amendments

Support for the amendments to claim 1 is found in claims 2 and 3, now canceled. Support for new claims 14-16 is found in claims 1-5 as filed. Support for new claims 12, 13, 17, and 18 is found in the specification at page 13, lines 15-19. Support for new claim 19 is found at page 3, lines 2-6. Support for new claims 20-22 is found in claim 2, as filed. No new matter is introduced by these amendments.

A "marked up" version of the claims showing the changes made and an appendix of the claims as pending are attached.

The Office Action

Claims 1-11 are pending in this application. Claims 1-11 stand rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. Claims 1-11 stand further rejected under 35 U.S.C. § 112, second paragraph, for indefiniteness.

Combined Declaration and Power of Attorney

The Examiner notes that the Declaration is defective. A corrected Combined Declaration and Power of Attorney is enclosed with this reply.

Rejections Under 35 U.S.C. § 112, first paragraph

Claims 1-11 stand rejected under U.S.C. § 112, first paragraph, for lack of enablement. The Examiner asserts that the specification fails to enable a person of ordinary skill in the art to practice the invention as claimed. The Examiner asserts several grounds of rejection, each of which is addressed below.

In asserting a lack of enablement rejection, the Examiner argues that (Final Office Action, page 3)

> even where there is no need or requirement to deliver therapeutic proteins to the brain and the invention is construed as cell therapy, it still depends on the *in vivo* expression of exogenous DNA.

Applicants respectfully note that, as presently amended, the claims do no longer require the *in vivo* expression of a therapeutic protein or exogenous DNA.

The invention as presently claimed encompasses an *in vitro* method for promoting stem cell differentiation into cells that are lineage-restricted to dopaminergic neurons. The exogenous DNA encoding a cell fate-inducing gene (e.g., Nurr-1 or PTX-3) is expressed *in vitro* to cause a cell fate determination. After the stem cells are lineage restricted, they are engrafted into the affected brain regions of the patient. Therefore, the claimed method does not treat a neurodegenerative disease by the *in vivo* expression of a heterologous gene or the *in vivo* differentiation of a transgenic stem cell. Thus, there is no requirement that the cells express the heterologous gene beyond the time required to induce a cell fate choice *in vitro*.

As described in the accompanying Declaration by one of the inventors, Dr. Ole Isacson, stem cells can be successfully lineage-restricted *in vitro* to dopaminergic neurons following transfection with a cell fate-inducing genes, Nurr-1 and PTX-3. Specifically, Dr. Isacson describes the results of transfecting D3 mouse blastocyst-derived embryonic stem cells with a vector expressing Nurr-1 or PTX-3. The methodology outlined by Dr. Isacson is identical to that disclosed in Examples 1 and 2 of the instant specification.

Further, Dr. Isacson describes successful results of transplanting Nurr-1-expressing ES cells using techniques that are substantially identical to those disclosed in the specification in Example 4.

Accordingly, Applicants respectfully submit that the specification enables a person of ordinary skill to practice the full scope of the presently claimed invention. This rejection may be withdrawn.

Rejections Under 35 U.S.C. § 112, second paragraph

Claims 1-11 stand rejected under U.S.C. § 112, second paragraph, for indefiniteness. Specifically, the Examiner asserts that the claim term "cell fate-inducing genes" is indefinite because the term is not defined in the specification. Applicants point out that the claims have been amended to remove the term "cell fate-inducing gene." Accordingly, this rejection should be withdrawn.

CONCLUSION

Applicants submit that the claims are in condition for allowance, and such action is requested. Enclosed is a petition to extend the period for replying for three months, to and including December 2, 2002, as November 30, 2002, falls on a Saturday. If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: December 2, 2002

Susan M. Michaud

Paul T. Clark
Reg. No. 30,162

Susan M. Michaud
Reg. No. 42,885

Clark & Elbing LLP
101 Federal Street
Boston, MA 02110
Telephone: 617-428-0200
Facsimile: 617-428-7045

Version With Markings to Show Changes Made

1. (Amended) A method of treating a human patient suffering from [a neurodegenerative] Parkinson's disease, said method comprising the steps of:

(a) obtaining one or more stem cells;

(b) transfecting said stem cells with Nurr-1;

(c) culturing said stem cells of step (b) to form cells which are lineage-restricted to dopaminergic neurons; and

(d) engrafting into said patient said lineage-restricted cells of step (c) [a population of recombinant cells comprising one or more cell fate-inducing genes that permit said cells to form neurons in said patient].

4. (Amended) The method of claim 1 [3], wherein step (c) [d)] comprises inducing cell division using a growth factor.

Claims as Pending

1. (Amended) A method of treating a human patient suffering from Parkinson's disease, said method comprising the steps of:

(a) obtaining one or more stem cells;

(b) transfecting said stem cells with Nurr-1;

(c) culturing said stem cells of step (b) to form cells which are lineage-restricted to dopaminergic neurons; and

(d) engrafting into said patient said lineage-restricted cells of step (c).

4. (Amended) The method of claim 1, wherein step (c) comprises inducing cell division using a growth factor.

5. The method of claim 4, wherein said growth factor is leukemia inhibitory factor.

12. (New) The method of claim 1, wherein step (c) further comprises culturing said stem cells in the presence of fibroblast growth factor-8 (FGF-8).

13. (New) The method of claim 1, wherein step (c) further comprises culturing said stem cells in the presence of sonic hedgehog (Shh).

14. (New) A method of treating a human patient suffering from Parkinson's disease, said method comprising the steps of:

(a) obtaining one or more stem cells;

(b) transfecting said stem cells with PTX-3;

(c) culturing said stem cells of step (b) to form cells which are lineage-restricted to dopaminergic neurons; and

(d) engrafting into said patient said lineage-restricted cells of step (c).

15. (New) The method of claim 14, wherein step (c) comprises inducing cell division using a growth factor.

16. (New) The method of claim 15, wherein said growth factor is leukemia inhibitory factor.

17. (New) The method of claim 15, wherein step (c) further comprises culturing said stem cells in the presence of fibroblast growth factor-8 (FGF-8).

18. (New) The method of claim 15, wherein step (c) further comprises culturing said stem cells in the presence of sonic hedgehog (Shh).

19. (New) A method of treating a human patient suffering from Parkinson's disease, said method comprising the steps of:

(a) providing cells which are lineage-restricted to dopaminergic neurons, and

(b) engrafting into said patient said lineage-restricted cells of step (a).

20. (New) The method of claim 19, wherein said cells are stem cells or are derived from stem cells transfected with Nurr-1.

21. (New) The method of claim 19, wherein said cells are stem cells or are derived from stem cells transfected with PTX-3.

22. (New) The method of claim 19, wherein said cells are stem cells or are derived from stem cells transfected with Nurr-1 and PTX.